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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/337,675	06/22/1999	RAJEEV A. JAIN	029318/0497	9275

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FOLEY & LARDNER
3000 K STREET, SUITE 500
WASHINGTON, DC 200075109

EXAMINER	
TRAN, SUSAN T	

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 03/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/337,675	JAIN ET AL.	
	Examiner	Art Unit	
	Susan T. Tran	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22 and 25-54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22 and 25-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *01/18/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 01/18/06 has been entered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-22 and 25-54 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. It appears that applicants' specification does not provide support for the amended limitation "wherein at least 50% of the drug particles have a particle size of less than about 1000 nm". Applicants' specification at page 14, 2nd paragraph defines "an effective average particle size of less than about 1000 nm" is "at least 50% of the drug/agent particles have an *average* particle size of

less than about 1000 nm". The specification further discloses "the mean diameter of 50% of the particles, D_{v50}, refers to the volume *average diameter* of 50% of the particles...".

Claims 10-12 and 54 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for controlling the release rate of drug, does not reasonably provide enablement for using polyvinyl pyrrolidone or polyethylene glycol alone is capable of controlling the release rate. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include:

1) The nature of the invention;

2) The state of the prior art;

3) The level of one of ordinary skill;

4) The level of predictability in the art;

5) The breadth of the claims;

6) The amount of direction or guidance provided by the inventor;

7) The existence of working examples; and

8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400,

1404 (Fed. Cir. 1988). When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation. These factors are discussed in detail as follow:

1) The nature of the invention: a solid dose controlled release nanoparticulate composition comprising at least one rate-controlling polymer including polyvinyl pyrrolidone, or polyethylene glycol.

2) The state of the prior art: the state of the art is very high in term of using polyvinyl pyrrolidone or polyethylene glycol in a controlled release dosage form.

3) The level of one of ordinary skill: the ordinary skill in the art is high (PhD level technology).

4) The level of predictability in the art: there is predictability in the art of the ability of using polyvinyl pyrrolidone or polyethylene glycol in the controlled release dosage form.

5) The breadth of the claims: the claims are broad (independent claims do not recite specific rate-controlling polymer).

6) The amount of direction or guidance provided by the inventor: applicants' specification fails to disclose how polyvinyl pyrrolidone or polyethylene glycol can be used singly as a rate-controlling polymer. Applicants' attention is called to the teaching on page 216 of Rong-Kun Chang (Sustained Drug Release from Tablets and Particles Through Coating) discloses polyvinyl pyrrolidone forms a rapidly dissolving barrier that results in premature diffusion of the drug and disintegration of the tablet. Chang further teaches that controlled release coatings can obtained by combining PVP and PEG with

a hydrophobic polymer to achieve slower release rate (page 238).

7) The existence of working examples: there are working examples in the specification, however, applicant fails to show the use of polyvinyl pyrrolidone or polyethylene glycol alone, as a rate-controlling polymer.

8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure: it would require an undue experimentation by one of ordinary skill in the art to use the invention commensurate in scope with the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 8-10, 13, 14, 30, 31 and 34-53 are rejected under 35 U.S.C. 102(b) as being anticipated by Desieno et al. US 5,573,783.

Desieno discloses a pharmaceutical film matrix comprising nanoparticles of a low solubility drug associated with a steric stabilizer (surface stabilizer), and over coated with a protective layer (abstract). Desieno also discloses the drug particles having extremely small effective average particle size can be prepared by wet milling in the presence of grinding media in conjunction with a surface modifier (column 2, lines 51-55). The effective average particle size is less than about 400 nm (column 6, lines 15-24). Suitable drug substances are disclosed in column 3, lines 16-46, which includes

naproxen and cyclosporin. The steric stabilizers are disclosed in column 3, lines 56-65, but the most preferred steric stabilizer is polyvinylpyrrolidone (column 4, lines 22-23). The protective layer over coated the film matrix comprises polyvinylpyrrolidone (PVP) and polyethylene glycol (PEG) (column 5, lines 1-13). Column 4, lines 42-67 discloses the process for preparing the nanoparticles, wherein water is used for the dissolution and suspensions steps is also disclosed. Examples 1 and 2 show the amounts of drug that falls within the claimed range.

It is noted that Desieno does not expressly teach the time period of controlled release from about 2 to about 24 hours. However, the time period is clearly inherent because Desieno uses the same rate-controlling polymer in the over coated protective layer, *e.g.*, polyethylene glycol and polyvinylpyrrolidone. Products of identical chemical composition cannot have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

It is noted that Desieno is silent as to the teaching of the particle size distribution (at least 50% of the drug particles have a particle size of less than about 1000 nm). However, it is the position of the examiner that if not at least 90%, then at least 50% of the drug substance taught by Desieno is less than 1000 nm because Desieno teaches an *effective average particle size* of a drug substance to be less than 400 nm (column 6, lines 15-50). The term "effective average particle size" is known in pharmaceutical art to have at least 50% of the total particle population (see for example Liversidge et al.,

column 5, lines 20-39). The term is also defined by the applicant at page 14, lines 12-17 as "at least 50% of the drug particle".

Claims 1, 2, 8, 9, 13, 14, 30, 31 and 34-38, 41, 42, 45, 46, 49, 50 and 53 are rejected under 35 U.S.C. 102(b) as being anticipated by Modi WO 95/22318.

Modi discloses a controlled release formulation comprising microspheres matrix made of polymer selected from starch, gelatin, polyvinyl alcohol, and cellulose derivatives, the microspheres are over coated with a copolymer to provide a controlled release over a period of days or even weeks (pages 3-4). The over coated is a copolymer of d,l lactide-glycolide in a 2% solution (page 8, lines 26-30). The microspheres have a particle size ranges from 100 nm to 100 μm (page 8, lines 23-25).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-22 and 25-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Desieno et al. and Liversidge et al. US 5,145,684, in view of Fiend et al. US 5,811,388.

Desieno is relied upon for the reason stated above. Desieno is silent as to the teaching of the particle distribution. However, it is well known in pharmaceutical art that the term "effective average particle" means at least 50% of the particle population. To be more significant, Liversidge teaches a dispersible particle made of a drug substance and a surface modifier adsorbed on the surface of the drug substance to maintain *an effective average particle size* of less than about 400 nm (abstract). The term "effective average particle size" is defined by Liversidge as at least 90% of the particle have an average particle size of less than 400 nm measured by using the technique that is so well known in pharmaceutical art (column 5, lines 20-39).

Desieno does not expressly teach the concentration of the rate-controlling polymer as well as the specific rate-controlling polymer claimed in claims 11 and 12, the binder and the lubricant claimed in claims 5-7.

Friend teaches a tablet dosage form made of matrix compose of drug dispersed in hydrocolloid and excipients (abstract, and column 5, lines 49-53). The excipients, such as binders, diluents, and lubricants are present at a level of from about 2-50% (column 11, lines 22-65). The excipients further include HPMC, PVP, and cellulosic derivatives (column 12, lines 1-33). Suitable lubricant, such as magnesium stearate are

mixed with the drug substance and HPMC and then compressed into tablet (column 17, lines 56-61). The tablet is further coated using enteric coating polymers selected from cellulose acetate phthalate, polyvinyl acetate phthalate, methacrylic acid, and those polymers having the trade name Eudragit in an amount of from about 0.5 to about 10% (column 14, lines 20-62). Thus, it would have been obvious for one of ordinary skill in the art to modify the nanoparticle of Desieno and Liversidge using the excipients and the enteric coating polymers in an effective amount in view of the teachings of Friend, because Friend teaches a tablet dosage form suitable for controlled release of poorly soluble drug substance. The expected result would a controlled release film matrix coated carrier that exhibits excellent bioavailability and extremely stable.

It is noted at column 14, lines 7-10, the inner composition which makes up the matrix of the tablet is free of any enteric polymeric material. However, the claims of the present invention do not exclude coating the rate controlling polymer on the surface nanoparticulate drug composition as taught by Friend and evidenced by applicants' claim 1 and 15.

Response to Arguments

Applicant's arguments filed 1/18/06 have been fully considered but they are not persuasive.

Applicant argues that Desieno does not teach or suggest nanoparticulate compositions that comprise at least one rate-controlling polymer. In response to applicant's argument, it is not necessary for the prior art to show each and every

property of the claimed product (see *In re Best*, Bolton and Shaw (CCPA) 195 USPQ 430, 10/13/1977). It is noted that Desieno recognizes the controlled release properties in the use of the claimed "rate controlling polymer", for example, Desieno at column 8, lines 44-45 discloses the drug particles of the invention decreased gastrointestinal irritancy; and at column 18, lines 4-8 discloses the PVP/PEG overcoat for compositions containing danazol, PVP and sodium lauryl sulfate coated on a bead, provides physical protection for the drug layer coated on the bead. Accordingly, the burden of proof is shifted to applicant to prove that the prior art products do not necessarily or inherently possess the characteristic (the controlled release of active agent) of the claimed product, because Desieno teaches the use of the claimed rate controlled release polymer. *In re Fitzgerald*, 619 F.2d 67, 70, 205 USPQ 594, 596 (CCPA 1980) (quoting *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433-34 (CCPA 1977)).

Applicant argues that the PVP/PEG overcoat taught by Desieno is not a rate-controlling polymer. However, the examiner is unable to determine the patentability distinct between the claimed PVP/PEG coat and the PVP/PEG over coat taught by Desieno. It is noted that products of identical chemical composition cannot have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, *the properties applicant discloses and/or claims are necessarily present*. *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

Applicant admits that PVP and PEG can be used in coating systems, but must be used in conjunction with a polymer that forms a water insoluble backbone, such as

poly(alkylmethacrylate) to yield a controlled release composition (page 19, 1st paragraph). Accordingly, there appears to be an enablement issue with the claims since they recite PVP and PEG alone, as a rate controlling polymer. Applicant's attention is called to claims 10 and 37. Claim 10 recites a Markush group of polymer that includes polyvinyl pyrrolidone. Claim 37 recites a Markush group of surface stabilizer that includes polyethylene glycols. Therefore, if polyvinyl pyrrolidone of claim 10 is selected, and polyethylene glycol of claim 37 is selected, would the claimed invention have the controlled release rate that is superior over those of Desieno? It is noted that applicants' claims do not require the present of hydrophobic polymer, such as poly(alkylmethacrylate). Accordingly, the rejection over Desieno is maintained.

Applicant argues that Modi does not teach at least one surface stabilizer is associated with the surface of the nanoparticulate drug. Contrary to the applicant's argument, Modi at page 5, lines 9-10, discloses adding surfactant before coating the microspheres with rate controlling polymer.

Applicant argues that Modi does not teach the solubility of the drug. In response to applicant's argument, Modi teaches incorporating drugs in general, to a controlled release system similar to that of the claimed invention. Modi does not teach the drugs have to be water-soluble. Accordingly, the drugs disclosed by Modi can include water soluble and water-insoluble drugs.

Applicant argues that Modi does not teach at least 50% of the drug particles have a particle size of less than about 1000 nm. However, as disclosed in the above 112, 1st rejection, it appears that there is no support in the specification for the limitation that at

least 50% of the drug particles have a particle size of less than about 1000 nm. What disclosed in applicant's specification appears to be average particle size. Modi teaches the particle having size of from 100 nm to 100 μm, more typically from 10 nm to 10 μm range. Accordingly, it is the position of the examiner that the average particle size of Modi would fall within the claimed range because Modi teaches microspheres in nanometer range, *e.g.*, from 10 nm. Therefore, the burden of proof is shifted to applicant to show that the microspheres of Modi does not have the claimed average particle size.

Applicant argues that there is no motivation to combine Desieno in view of Liversidge and Friend. To clarify the record, the 103(a) rejection uses Desieno as a primary reference, in view of Liversidge and Friend. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Liversidge is cited solely for the teaching of particle distribution and the meaning of "effective average particle size". Friend is cited solely for the teaching of the concentration of the rate-controlling polymer as well as the specific rate-controlling polymer claimed in claims 11 and 12, the binder and the lubricant claimed in claims 5-7. The test for obviousness is not whether the features of

a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

Pertinent Arts

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Curtet et al., and Rong-Kun Chang are cited as of interest for the teaching of co-micronizing hydrophobic drug with surfactant to increase bioavailability, as well as for the teaching of sustained drug release formulations.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan T. Tran whose telephone number is (571) 272-0606. The examiner can normally be reached on M-R from 6:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K. Page, can be reached at (571) 272-0602. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for

published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

S. Tran
Patent Examiner
AU 1615